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Cardiac Magnetic Resonance Imaging The Case for Nonionizing Radiation Protection and the Precautionary Principle

Philipp A. Kaufmann, MD

The use of noninvasive cardiac imaging to detect heart disease to guide therapy has grown substantially during the past decade. To date, imaging tests using ultrasound or magnetic fields have been perceived as safer alternatives compared with well-established and widely used tests, which use ionizing radiation such as computed tomography and nuclear imaging. For the latter, many efforts have been done to reduce radiation exposure to the patients and despite substantial advancements even more efforts will be needed to further reduce radiation exposure.^{1,2}

See Article by Lancellotti et al

By using a static and a gradient magnetic field in combination with a radiofrequency field, magnetic resonance (MR) provides excellent contrast among different tissues of the body, including the brain, the musculoskeletal system, and the heart. Cardiac MR (CMR) imaging has evolved from a premature technique into a tool with the potential to find an important clinical role in the near future for the noninvasive assessment of morphological and functional aspects of the heart. Consequently, CMR belongs to the fastest growing new fields of broad MR application. At the same time, CMR uses some of the strongest and fastest switching electromagnetic gradients available in MR imaging.^{3,4} The amount of radiofrequency field energy delivered is defined as the specific absorption rate. Although long-term effects on human health from exposure to strong static magnetic fields seem unlikely,⁵ acute effects such as vertigo, nausea, change in blood pressure, reversible arrhythmia,⁶ and neurobehavioral effects have been documented from occupational exposure to 1.5 T.⁷ Studies focusing on experimental teratogenic^{8–12} or carcinogenic^{13–15} effects of MR have demonstrated conflicting results. However, recently concerns about potential genotoxic effects of MR imaging have been raised.^{16,17} On the basis of a growing body of literature showing in vitro and in vivo^{3,16,18} data supporting both exposure time-dependent as well as dose-related effects of magnetic fields on DNA

integrity, the International Agency for Research on Cancer (IARC) has classified (extremely low) gradient fields generated during MR scanning as possible human carcinogen (group 2B).¹⁹ Similarly, the European Parliament²⁰ as well as the International Commission on Non-Ionizing Radiation Protection (ICNIRP)²¹ and the World Health Organization (WHO)²² have urgently called for an action to evaluate adverse biological effects of clinical MR scanning.

In fact, several laboratories have independently and consistently observed an increase in DNA double-strand breaks (DSBs) after CMR scanning by the use of a broad spectrum of methods, such as histone γ -H2AX phosphorylation, comet assay, or micronuclei.^{3,23–25} However, although Simi et al³ have reported on persistence of DSB ≤ 24 hours after CMR exposure, most other studies did not address the persistence of the DSB induced by CMR, although this is a key issue of genetic risk assessment as DNA damage can trigger DNA instability and exert potential carcinogenic effects. It is in this context that Lancellotti et al,²⁶ in this issue of *Circulation: Cardiovascular Imaging*, have studied an important aspect of the impact of CMR scanning on peripheral lymphocyte DNA integrity, namely the time course over 1 year. Their results are remarkable for several reasons. First, they studied CMR alone with no gadolinium-based contrast medium to avoid confounding effects from the genotoxic contrast medium. As the latter, however, is widely used off-label in the vast majority of clinical CMR scans,²⁷ the findings may be even more relevant in the clinical setting. Second, they did not find any DNA damage early after CMR but observed an increase in DSB from day 2 until the first month, which disappeared after 1 year. Third, they found that CMR was also associated with a minor but significant immediate blood cell alteration reflecting inflammatory response. This adds a new aspect to the knowledge of biological reactions to CMR exposure.

Several putative mechanisms by which MR may increase DSB have been published, mainly focusing on impairment of repair mechanisms, for example by activation of oxidative stress pathways²⁸ or initiation of transcription by interacting with moving electrons in DNA by generating repulsive (Lorentz) forces causing chain separation at specific DNA sequences.²⁹ As opposed to ionizing radiation with direct damage to the DNA, the impairment of repair mechanisms may require more time before an increase in DSB can be measured. This would support why the authors found a delay between CMR exposure and DNA damage. The authors suggest that previous studies had found a somewhat earlier increase in DSB because patients were also exposed to gadolinium,^{3,23} which has been shown to potentiate the genotoxic effect of CMR³⁰ but still requires some delay after CMR exposure.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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According to this delay hypothesis, immediate post-CMR measurements would not detect DNA damage. This fits well with recent results by Brand et al³¹ who failed to detect DSB induction as early as 5 minutes after CMR exposure.

Another key finding in the study by Lancellotti et al,²⁶ which supports a causal relationship between DNA damage and CMR is the strong and impressive correlation between the augmentation of γ -H2AX levels at 1 month and the specific absorption rate values. This dose–response relation in the clinical setting was the final missing link closing the causal gap of knowledge about DSB induction and CMR scanning.

Despite the important information provided by the study of Lancellotti et al,²⁶ many questions remain unanswered. As the vast majority of CMR scans involve gadolinium-based contrast application more information on the interaction of gadolinium with CMR with regard to DNA damage and its time course would be of great clinical interest. Moreover, with the available data one cannot comment on the long-term clinical impact of the DNA damage caused by nonionizing radiation and it is foreseeable that such information will most probably be difficult to acquire. Even for ionizing radiation from diagnostic procedures, no direct observational proof of its adverse impact on outcome is available because of the small scale of damage and the long delay between exposure and event. Estimations of the increased risk of cancer after low-dose radiation are based on extrapolations from population cohorts exposed to larger radiation doses,¹⁶ such as atomic bomb survivors (who were also exposed to a nuclear electromagnetic pulse). Although the results by Lancellotti et al²⁶ may not answer all questions, they do increase the awareness of potential hazards of CMR. We need to be aware of the potential association of any type of radiation (ionizing or non-ionizing) with cancer³² because one cannot predict the risk in individual patients, and because clinically significant consequences may not become evident for many years. That is why the authors suggest applying the precautionary principle also to CMR, concurring with other experts.³³ Increased awareness of this potential association should stimulate more research so that the medical and imaging community can fully understand the biological effects of nuclear MR imaging.

Disclosures

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KEY WORDS: Editorials ■ magnetic resonance imaging ■ radiation protection